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MAIL STOP PROVISIONAL PATENT APPLICATION
Attorney Docket No. 26051

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Domb et al

Serial No. NOT YET ASSIGNED

Filed: March 4, 2004

For: **SAFE DEVICE FOR IONTOPHORETIC DELIVERY OF DRUGS**

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submitted herewith for filing in the U.S. Patent and Trademark Office is the following **PROVISIONAL APPLICATION:**

(1) Transmittal Letter
(2) Cover sheet for filing **Provisional Application**
(3) 15 page Provisional Application consisting of:
12 pages Textual Specification,
2 pages of Claims,
0 page of the Abstract,
1 sheet of Drawings;
(4) Check No. 20573 $ 80.00 for filing fee as a small entity;
(5) Postcard for early notification of serial number.

The Commissioner is hereby authorized to charge any deficiency or credit any excess to Deposit Account No. 14-0112.

Respectfully submitted,
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)		
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Additional inventors are being named on the 2ND *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

SAFE DEVICE FOR IONTOPHORETIC DELIVERY OF DRUGS

CORRESPONDENCE ADDRESS

Direct all correspondence to:

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OR

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 14
☑ Drawing(s) *Number of Sheets* 1
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Respectfully submitted,

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Date March 4, 2004

REGISTRATION NO. 47,421 *(if appropriate)*

Docket Number: 26051

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Number 2 of 2

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SAFE DEVICE FOR IONTOPHORETIC DELIVERY OF DRUGS

Iontophoresis is a noninvasive technique, in which an electric current is used to enhance the penetration of charged drugs to a tissue [1].

Iontophoresis has been used in various fields of medicine, including transdermal administration of local anesthetics [2], testing for cystic fibrosis by transcutaneous delivery of pilocarpine [3], administration of vidarabine to patients with herpes orolabialis [4], fluoride administration to patients with hypersensitive dentin [5], and gentamicin administration for bacterial otitis [6].

Transcorneal or transscleral iontophoresis of various charged drugs have been reported [7-11]. High levels of antibiotics were measured in the cornea and aqueous humor after transcorneal iontophoresis, compared with topical application or subconjunctival and intravenous injection which do not achieve adequate drug levels and involve other complications [7-11]. Moreover, published data confirm that high drug concentrations penetrate also the posterior segments of the eye after transscleral iontophoresis, allowing the treatment of posterior disorders of the eye, such as posterior uveitis and endophthalmitis [12-25]. These studies used iontophoresis of drug solution, which is technically clumsy, may cause mechanical injuries to the cornea and demands sterilization of the solution and cup before each treatment.

While iontophoresis has been developed for the eye, little attention was given to the toxicity of the iontophoresis to the eye.

In addition, in most reports, patents and applications, as listed below, there is no distinction between the sights on the eye where the iontophoresis is applied. The following is a summary of the prior art related to this invention:

US patent 4,564,016 describes an iontophoretic device using a solution chamber where current flow is adjusted to a desired value by adjusting a

potentiometer for a flow passage of a diameter of 0.25 to 0.5 millimeters, which is equivalent to a range of current density of 200 milliampere to 2000 milliamperes per cm^2. This is a huge amount of current that may electrify the patient or at least cause a significant damage to the eye.

In WO 91/12049, an iontophoretic system for focal transcleral destruction of living human tissue for the purpose of immediate decreasing eye pressure is described. A current of about 3.0-4.0 milliamperes for about 30 seconds to 5 minutes is applied in dozens locations on the sclera. The surface area that this apparatus is applied for is in the range of 0.2 to 2 mm, preferably 0.3-0.6 mm in diameter which translates to about 0.3 mm^2 or a current of about 1200 milliampers per cm^2.

In another publication, Barza M, Peckman C, Baum J. in Ophthalmology. 1986 Jan; 93(1):133-9, transscleral iontophoresis of cefazolin, ticarcillin, and gentamicin in the rabbit is described. The authors applied 2 milliampers for 10 minutes and were able to achieve mean vitreal concentrations of cefazolin, ticarcillin, and gentamicin of 94-207 micrograms/ml in the normal rabbit eye. The current density applied onto the sclera, in this publication is in the range of 100-200 milliamperes/cm^2. After 10 minutes of such application, no doubt that a high amount of drug is found in the inner parts of the eye as the process drilled a hole in the sclera.

Another publication by Maurice DM, in Ophthalmology. 1986 Jan; 93(1):128-32, Iontophoresis of fluorescein into the posterior segment of the rabbit eye is described. As stated in the article, iontophoresis of appreciable quantities of fluorescein into the vitreous body of the rabbit results from the use of a high electrical current density over a limited area of the globe. This is achieved by passing current through the fluorescein when it is held against the region of the ora serrata in a tube less than 1 mm in diameter. The retina is destroyed over a corresponding area when the current enters the eye. Again, current densities of over 100 milliamperes/cm^2 was applied to the sclera and caused damage while inserting a high dose of drug.

Iomed, Inc. in a series of patents and applications as specified below, describe the use of iontophoresis for the delivery of drugs such as methotrexate, proteins, VEGF inhibitor, and 5-FU.

WO 02/058789 describes a device for the delivery of interferon where the drug is dissolved in a solution and held in a reservoir made of a permeable envelop which may contain an amorphous gel. A current of 0.5 to 4 milliamperes is applied for 5 to 20 minutes.

In WO 03/008036 a similar device is described for the delivery of steroids to the eye using a current of 0.5 to 4 milliamperes applied for 5 to 20 minutes.

WO 03/007961 describes the same device for the delivery of methotrexate and it derivatives for treating neoplastic, angiogenic and immunosuppressive ocular irregularities. A current of 0.5 to 4 milliamperes for 1-60 minutes is used in this publication.

Other applications to Iomed with a similar text but different drugs include: WO 03/007798 for the delivery of 5-fluorouracil for the same indications using a current of 0.5 – 5.0 for 1-60 minutes; WO 02/058786 for the delivery of aptamer that inhibit VEGF function using a current of 0.5 to 4 milliamperes for 1-60 minutes. In US 2003/0092774 A1, the same authors describe the same system but for the delivery of Cobrestatin as neoplastic drug for treating cancer of the skin and eye. Again a current of 0.1-5 for 1-60 min is mentioned.

In EP 1199084A2 a similar device is described with a reservoir of the drug solution with a punctuation of 0.03 cm^2.

EP 0927 560 A1 described a reservoir clumsy system for iontophoresis to the eye using drug solution running in the circular element that is vacuum stick to the entire eye surface. A current density of 0.5-5 milliamperes/cm^2 as estimate is mentioned in this publication.

EP1201265A1 describes a complicated iontophoretic apparatus with a drug chamber or cup and a membrane that retains the drug solution from dripping from the device. The device can be applied on any part of the eye.

WO 03/043689 A1 to Optis describes an apparatus with a cup to maintain the drug solution that can be used for electroporation and injecting solutions to the eye. WO 02/083184 A2 to Optis describes an iontophoresis of DNA into cells or tissue with no relation to iontophoresis to the eye.

WO 99/40967, describing an invention invented by one of the present inventors, describes the delivery of drugs to the eye using solid hydrogel discs of a size of 3 millimeter in diameter applying onto the cornea a current of up to 1 milliamper which is translated to about 14 milliamperes/cm^2.

In scientific reports in which transcorneal iontophoresis at a current density of 20 milliamperes/cm^2 for 5 minutes was found to be non harmful to the cornea [L. Hughes and D. M. Maurice, *Arch Ophthalmol.* 102, 1825 (1984)], and transscleral iontophoresis at a current density inferior 50 milliamperes/cm^2 is practically safe [F. F. Behar-Cohen, A. El Aouni, S. Gautier, G. David, J. Davis, P. Chapon and J. M. Parel, *Exp Eye Res.* 74, 51 (2002)]. These publications however, were on iontophoretic devices using eye-cup solution of drugs.

It is clear from the prior art described above that very little attention was given to the safety of iontophoresis process to the eye surface and the health of the patient. Moreover, based on the prior art one may apply a current of as high as 2000 milliamperes that may electrify the patient and the assistant applying the treatment. Also, no information was given on the sensitivity differences between the sclera, cornea and other parts of the eye surface that is relevant to the current density possible to apply without causing damage to the eye. Furthermore, in recent and old prior art there is little attention, if at all, to the difference between current and current density.

The current applied in the prior art publications is given in terms of milliamperes or microamperes without any relation to surface area, i.e. square centimeter or millimeter, the current is applied on. The ratio of current to surface area, i.e current density, is the proper definition of the actual current applied to the tissue which has relevance to toxicity and efficacy of iontophoresis applied.

It is therefore the objective of this invention to provide a safe iontophoresis guidelines and apparatus for safe iontophoresis to the cornea and to the sclera as well other sites on the eye surface. It should be noted that there are significant differences between the cornea tissues and function and the sclera. Any damage to the cornea surface immediately affects the vision and comfort of the patient which is less pronounced when applied to sclera. In general, the sclera is coated by the conjuctival tissue which protects the sclera where the cornea is not. The clarity of the cornea is very important as it is essential for interaction with light while the sclera is not relevant for light interaction.

It is therefore the objective of this invention to provide an iontophoretic device that provides the proper safe amount of current to various parts of the eye in terms of current applied per unit of surface area of the eye exposed to the current.

Thus, the present invention provides a device for iontophoretic delivery of a drug to a tissue, and includes an arrangement that prevents operation of the device at a current density that is higher than a predetermined value.

The term *current density* denotes the ratio between the current used to enhance the penetration of drug to the tissue and the surface area of tissue to which current is applied.

Typically, the arrangement includes a processor responsive to data that is indicative to the surface area. The processor response is to set the maximal current allowed at the given surface area.

In accordance with one embodiment of the present invention, the operator of the device inputs into the device data that is indicative to the surface area. For instance, the operator may input a code, which is indicative of the surface area of a contacting member, which contacts a drug-containing sponge with the tissue. The code may be imprinted on the contacting member, may be the sponge color, and the like.

The term *"sponge"* is used herein to denote a porous article made from hydrophilic or non-hydrophilic polymer, in which the porous structure allows it

to absorb and hold at least 30% w/w aqueous solutions without dissolving or disintegrating.

Non-limiting examples to such non-hydrophilic polymers are polystyrene, polymethacrylates, silicones and urethanes.

Hydrophilic sponges, are termed herein *hydrogel,* and have functional groups that associate well with water molecules such as hydroxy, ether, amide, thiol, carboxylic acid, amine groups and the like. Non-limiting examples to such hydrophilic polymers are crosslinked hydroethylmethacrylate (HEMA) and other hydrophilic acrylate and methacrylate monomers, polyethylene glycol, crosslinked polysaccharides and proteins, and polyvinyl pyrrolidone. Swellable hydrophilic-hydrophobic copolymers such as HEMA-methyl methacrylate copolymers may also serve as sponge material.

In accordance with another embodiment, the contacting member transmits a signal indicative of its surface area, and this signal is received by a receiving element that is in communication with the processor.

The processor may include a microprocessor programmed with a table including predetermined values of maximal current as function of the surface area or as function of the data indicative thereof. Alternatively, there may be mechanical or electrical arrangements that directly conjugate between the data indicative of the surface area and the maximal current allowed.

The maximal current density allowed may differ from one tissue to another, and therefore, preferably, the processor is also responsive to data indicative of the tissue to be treated.

For instance, a device according to the invention may be designed specifically for iontophoretic administration of drugs to the eye, where application of too large current density might cause irreversible damage to the eye tissue.

Various parts of the eye, may tolerate different current densities, and accordingly, one embodiment of the invention includes a processor that is responsive to data indicative of the different tissue to which INT is applied. For

instance, the operator may input the kind of tissue that is treated, and the microprocessor is programmed with various tables, each corresponding to a different tissue.

According to a specific embodiment of the invention, the arrangement is further capable of determining the maximal operation duration as function of current density, and preferably also as a function of the tissue to be treated.

According to one specific embodiment there is provided a device for iontophoretic administration of charged drugs to the eye comprising:

- an applicator formed with a receiving portion adapted for holding a replaceable sponge loaded with said charged drugs and allowing contact of the sponge with a surface of the eye;
- a data input element, allowing to input thereby data indicative to the size of the sponge;
- an electric current generating element, for generating currents not higher than a predetermined value, being electrically coupled to said receiving portion such that the current once generated passes through the sponge in a direction essentially normal to said surface of the eye;
- a processor capable of determining said predetermined value in accordance with the data inputted by said data input element.

Preferably, such a device also includes a second data input element allowing to input thereby the specific eye tissue to be treated (for instance, sclera or cornea) and said processor is capable of determining said predetermined value in accordance with this data and in accordance with the data indicative of the sponge size.

The term *"charged drugs"* refers to pharmaceutical compositions which may be *a priori* charged, to drugs which become charged in a solution with which the sponge is loaded, as well as to drugs which are initially not charged but become charged in the presence of an electrical current.

The term *"charged drugs"* refers also to complexed bioactive agents, bioactive agents conjugated to small or large molecules or polymers, and to bioactive agents encapsulated in a charged particle having a sub-micrometric size, whether the bioactive agent is charged or not.

Examples of commonly used charged drugs include antibiotics, such as gentamicin, tobramycin and vancomycin; antifungal drugs including miconazole, ketoconazole and omeprazol; anti-inflammatory agents such as ibuprofen and its derivatives, timolol; water soluble steroids such as dexamethasone phosphate and hydrocortisone succinate; anticancer agents such as mitomicin C, methotrexate and 5-fluorouracil; local anesthetics which are delivered to the oral cavity to anesthetize the gingival of tooth before a treatment or to reduce pain, such as lidocaine, bupivacaine and benoxinate.

Reference is now made to **Figure 1**, which shows a schematic representation of a device **30** according to one embodiment of the invention. The device **30** has a receiving portion **31** composed of an L-shaped arm **32** extending from the body of the device, and an adjustable ring **33**, which claps a sponge **34**. Ring **33** may accommodate sponge discs of various dimensions, by adjusting, with screw **35**, the diameter of the ring. The container of the device **36**, contains its electronic components. More specifically, it has an on/off switch **37**, and a push button **38**, which when touched gives pulses of a pre-set length and magnitude. The device has a time control button **39** and a digital time display window **40**, a current control button **41**, and a digital current display window **42**. The device has also a sponge size selection button **44** and a tissue selection button **46**.

The passive electrode of the device **43** is connected to the device **30** by a wire **50**.

In operation, the operator (not shown) turns on the On/off button **37** and inputs data indicative to the size of the sponge **34** by switching selection button **44** to S, M, or L (standing for small, medium, and large) and data indicative of the tissue to be treated by switching selection button **46** to C (cornea) or S (sclera). If sclera is chosed, the maximal current density allowed is 30 milliamperes/cm^2, and if cornea 20 milliampers/cm^2. If the current denstiy as computed by the processor (not shown) in accordance with the data indicative of the sponge size and the current chosen with button **39** is higher than the appropriate maximal value, touching push-on button **38** does not activate the device, but rather a light alert **52**, which indicates that the required current should not be applied to the chosen tissue with a sponge of the indicated size. If the computed current density is smaller than the maximal one allowed, the cureent passes for the time indicated in the time display window **40**. After relevant parameters are selected with selection buttons **44** and **46**, the sponge **34** is placed on the eye tissue that has to be treated (not shown), and electrode **43** is placed on any external part of the patient, for example, the ear, cheek, in his mouth, etc. the touch-on button **38** is touched to operate the device and deliver the drug to the tissue.

Toxicity experiment:

In a typical experiment, healthy New Zealand white male rabbits (n=13) weighting 2.0-3.0 kg are used. The animals are anesthetized by injection of ketamine and xylazine solution (1M, 25 and 2.5 mg/kg, respectively). Groups of 4 rabbits were used in this study (n=4) treated with transconjunctival iontophoresis, transscleral iontophoresis (after removal of the conjuctival coating tissue) using increasing current intensities for 1, 2, and 4 minutes using gentamicin sulfate loaded HEMA sponges prepared from the copolymerization of hydroxyethyl methacrylate (HEMA) and ethylene glycol dimethacrylate

(EGDMA) as crosslinker at a mole ratio of 99:1 using persulfate redox initiator, and a handy iontophoretic device with current and time controlled. The hydrogel disc probe contained an average amount of 26.0 mg gentamicin sulfate. Before placing of the electrode on the ocular surface, eye is topically anesthetized with 0.4% benoxinate eye drops (Localin®, Dr. Fischer Ltd., Israel). The gentamicin-loaded hydrogel disc (5x5 mm discs) is inserted into the cylindrical well of the iontophoretic device and placed onto the conjunctiva at the pars plana area. The complementary electrode is attached to the ear of the rabbit by means of an alligator clip. The iontophoretic administration was performed on one eye with a current intensity of 0.5, 1, 2 and 3 milliampers (2.5, 5.1, 10.2 and 15.3 milliampers/cm^2) for 1, 2, and 4 minutes. The corneal toxicity was examined. Iontophoresis onto the cornea rabbit eye did not affect the cornea at the low current dose of 2.5 milliampers/cm^2, the dose of 5.1 for 4 minutes caused a reversible swelling of the cornea which lasted a few hours after application. The 10.2 milliampers/cm^2 for 4 minutes also caused swelling and irritation to the surface of the cornea which become to normal after a few days. Higher current intensity caused pronounced damage to the cornea and thus is not recommended. As for the conjuctival iontophoresis, is was found that the cornea can be treated for 4 minutes with a current density of 20 milliampers/cm^2 with minimal reversible swelling and local irritation. Although higher current density can be applied up to about 25 milliampers/cm^2, this is not recommended due to discomfort and temporary toxicity to the sclera. Similar studies with gels loaded with saline resulted in similar results, where the iontophoresis for cornea and sclera were found safe to at least 15 milliampers/cm^2 for cornea and 20 milliampers/cm^2 for the scleral iontophoresis.

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CLAIMS:

1. A device for iontophoretic delivery of a drug either to or into a tissue, comprising an arrangement that prevents operation of the device at a current density that is higher than a predetermined value, said arrangement including means responsive to data that is indicative to the surface area through which the current is to pass, as to set the maximal current allowed at the surface area indicated by said data.

2. A device according to claim 1, including input means for manually inputting data that is indicative to the surface area.

3. A device according to claim 2, wherein said data is a code, which is indicative of the surface area through which current is passed to the tissue.

4. A device according to claim 2 comprising a contacting member capable of contacting a drug-containing sponge with the tissue to be treated, and said contacting member is capable of transmitting a signal indicative of its surface area, and a receiving element, capable of receiving said signal and being in communication with said means.

5. A device according to claim 1, including a microprocessor programmed with a table including predetermined values of maximal current as function of the surface area or as function of the data indicative thereof.

6. A device according to claim 1, wherein said means is also responsive to data indicative of the tissue to be treated.

7. A device according to claim 6, designed specifically for iontophoretic administration of charged drugs to the eye.

8. A device according to claim 7 comprising:

- an applicator formed with a receiving portion adapted for holding a replaceable sponge loaded with said charged drug and allowing contact of the sponge with a surface of the eye;
- a data input element, allowing to input thereby data indicative to the size of the sponge;

- an electric current generating element, for generating currents not higher than a predetermined value, being electrically coupled to said receiving portion such that the current once generated passes through the sponge carrier in a direction essentially normal to said surface;
- a processor capable of determining said predetermined value in accordance with the data inputted by said data input element.

9. A device according to claim 8, further comprising a second data input element allowing to input thereby the specific eye tissue to be treated and said processor is being capable of determining said predetermined value in accordance with this data and in accordance with the data indicative of the sponge size.

10. A device according to claim 1, wherein said arrangement further includes means for setting a maximal current duration in accordance with the current density.

11. A device according to claim 1, wherein said means is a processor.

12. A device according to claim 11, wherein said means is a microprocessor.

13. A device according to claim 1, including a microprocessor programmed with a table including predetermined values of maximal duration as function of the current density and/or as function of the tissue to be treated.

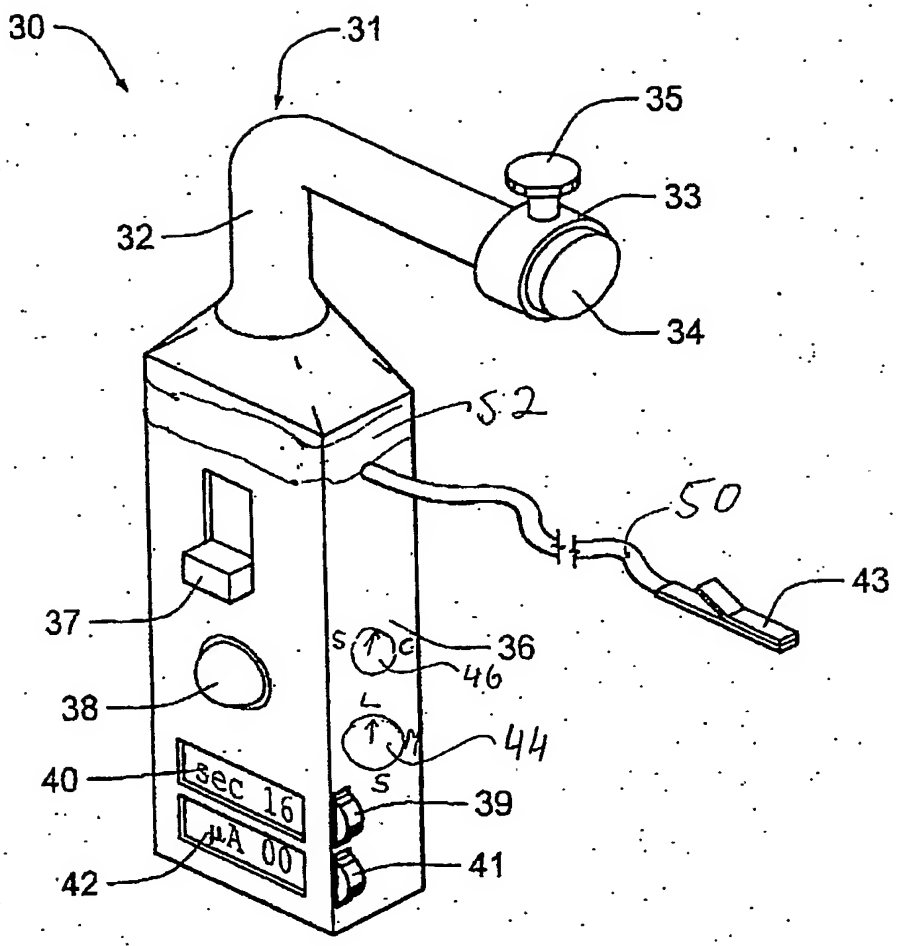

Fig. 1